REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, Claims 58-70 were pending in this application. With this amendment, Claims 58-66 has been amended, and Claim 67 has been canceled without prejudice. Claims 58-66 and 68-70 are pending after entry of the instant amendment.

Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Specification

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code.

Further, Applicants have amended the specification to correct the ATCC address on page 372, line 34 and the paragraph beginning at page 374, line 32, has been amended to comply with the provisions of the Budapest Treaty.

Double Patenting

The pending claims stand rejected under double patenting. In particular, the Examiner alleges that "there is at least one other application filed by the applicants which contains the polypeptide of SEQ ID NO: 16 which is identical to the polypeptide of SEQ ID NO: 7, and which contain possible conflicting claims." The Examiner further states that "applicant is required to point out to the Examiner all double patenting issues."

To our best knowledge, Applicants have not filed any applications having claims directed to a polypeptide of a sequence identical to SEQ ID NO: 7. Applicants believe that the Examiner reached his conclusion of the existence of possible conflicting claims based on the disclosure of the publications of other U.S. applications filed by Applicants, which do not reflect the changes made in preliminary amendments in those applications.

Accordingly, Applicants request that claim rejections under double patenting be

withdrawn.

Formal Matters

Applicants thank the Examiner for acknowledging that the deposit of organisms under accession number ATCC 209786 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure is in compliance with the deposit requirement.

Priority Determination

The Examiner asserts that the effective filing date for the application is October 15, 2001, the actual filing date of the instant application, and that Applicants are not entitled to claim priority to earlier-filed applications because they do not meet the requirements of 35 U.S.C. §112, first paragraph.

As discussed below, Applicants rely on the gene amplification assay (Example 114) for patentable utility which was first disclosed in International Application No. PCT/US00/03565, filed February 11, 2000, priority to which has been claimed in this application.

As will be shown, the disclosure of the instant application, which is similar to that of the earlier-filed application, provides the support required to establish utility for the claimed protein, for example, in detecting over-expression or absence of expression of the PRO274 polypeptide. Hence, Applicants respectfully submit that the effective filing date of the present application is February 11, 2000.

In support, Applicants enclose herewith pages 138-163, describing the gene amplification assay (Example 26), of WO 01/53486, corresponding to PCT Application PCT/US00/03565.

Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)

Claims 58-70 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." The Examiner specifically notes that "[t]here is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that

is disclosed as being associated with PRO274." Further, the Examiner asserts that because "PRO274 was amplified in only a very small number of tumors of the same type", for example, one (LT4) out of nine human lung tumor adenocarcinoma tumors and two (LT16 and LT18) out of nine human lung tumor squamous cell carcinomas, "the data do not support the implicit conclusion of the specification that PRO274 show s a positive correlation with lung cancer, much less that the levels of PRO274 would be diagnositic of such."

Claims 58-70 are further rejected under 35 U.S.C. §112, first paragraph, allegedly because one skilled in the art would not know how to use the claimed invention "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

For the reasons outlined below, Applicants respectfully disagree and traverse the rejections.

Applicants submit that the cancellation of Claim 67 renders the rejection of this claim moot. With respect to Claims 58-66 and 68-70, Applicants submit, as discussed below, that the Examiner has not established a *prima facie* case for lack of utility for PRO274 polypeptide.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office

personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. §2107 II (B) (1) (ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The PTO also sets forth the evidentiary standard as to utility rejections. In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. §101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a

preponderance of the totality of the evidence under consideration. *In re* Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

Proper Application of the Legal Standard

As discussed above, Applicants rely on the gene amplification data for patentable utility for the PRO274 polypeptide.

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 114 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9, including primary lung cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9. Further, Example 114 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc. PRO274 showed approximately 1.00-1.61 ΔCt units which corresponds to $2^{1.00}$ -$2^{1.61}$ fold amplification or 2.0 fold to 3.053-fold amplification in three types of human primary lung tumors, which is significant and thus the PRO274 gene has utility as a diagnostic marker of lung cancer.

Regarding the Examiner assertion that because PRO274 was amplified in only a very small number of tumors of the same type, thus the data did not support the implicit conclusion of the specification that PRO274 showed a positive correlation with lung cancer, much less that the levels of PRO274 would be diagnostic of such, Applicants respectfully disagree.

In response, Applicants respectfully submit a Declaration signed by Dr. Thomas D. Wu.

Dr. Wu studied microarray data from various types of human lung tumors for PRO274 mRNA expression levels. In particular, types of lung tumors Dr. Wu studied included (1) squamous cell carcinoma, (2) adenocarcinoma, (3) carinoma, large cell, (4) carcinoma, small cell and (5) carcinoma, unspecified non-small cell.

As stated in the Declaration, Dr. Wu found that for each type of the lung tumors listed above, the mRNA expression level of PRO274 was at least 10% or greater in the lung tumor tissues compared to normal lung tissues. Furthermore, on page 3 of the Declaration, Dr. Wu states:

> It is my considered opinion that when, the mRNA of a gene is overexpressed in at least about 10% of the lung tumors of the same type, the gene is biologically significant as a lung tumor marker. It is well known in the art that a lung tumor marker that is uniformly expressed in each type of lung tumor is very rare. Therefore, a gene that is overexpressed in at least 10% of a type of lung tumor would have a positive correlation with lung tumors.

Therefore, Dr. Wu concludes:

> It is my considered scientific opinion that identifying patients having a gene, such as PRO274 gene that is overexpressed in at least 10% of the lung cancer patients, would provide significant information for diagnosis and treatment since it would enable more accurate tumor classification and hence better determination of a suitable therapy.

Further, Applicants submit that the cell surface markers vary among the different types of tumor cells and cell lines. Some PRO polypeptides may be tested positive in a majority of the tested tumors and tumor cell lines, suggesting that they function as universal lung tumor markers for a variety of types lung tumors. On the other hand, some PRO polypeptides, such as PRO274, may be tested positive only in a limited number of lung tumors and tumor cell lines. As Dr. Wu suggested in his Declaration, a universal lung tumor marker is very rare. Accordingly, Applicants respectfully submit that genes encoding PRO polypeptides, such as PRO274, that are only amplified in a limited number (*i.e.*, ≥10% of the samples) of lung tumors can still be used as a cancer marker. Accordingly, Applicants believe that the Examiner has erroneously concluded that the present data do not support a correlation between PRO274 and lung tumor.

Applicants respectfully submit that it is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey D. Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey D. Goddard clearly establishes that the TaqMan real-time PCR method described in Example 114 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO274 is a diagnostic marker of human lung cancer.

A *prima facie* case of lack of utility has not been established

The Examiner bases the assertion, that increases in gene copy number do not reliably correlate with increased gene expression or polypeptide expression, on literature reports like Pennica *et al.* and Gygi *et al.*

According to the quoted statement relied on by the Examiner from Pennica *et al.*, "WISP-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression

in normal colonic mucosa from the same patient." From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, a correlation between DNA amplification and over-expression of polypeptide **was observed** in the case of WISP-1.

Further, the Examiner cites the Gygi *et al.* reference to establish that "even if gene amplification correlates with increased transcription, it does not always follow that protein levels are also amplified." The Examiner adds that "Gygi *et al.* studied 150 proteins... and found no strong correlation between proteins and transcript levels." Applicants respectfully traverse and point out that, on the contrary, Gygi *et al.* never indicate that the correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient in *accurately* predicting protein level from the level of the corresponding mRNA transcript (see page 1720, Abstract). Contrary to the Examiner's statement, the Gygi data indicate a general trend of correlation between protein [expression] and transcript levels. For example, as shown in Figure 5, the mRNA abundance of about 250-300 copies /cell correlates with the protein abundance of about 500-1000 x 10^3 copies/cell. The mRNA abundance of about 100-200 copies/cell correlates with the protein abundance of about 250-500 x 10^3 copies/cell. Therefore, high levels of mRNA generally correlate with high levels of proteins. In fact, most data points in Figure 5 followed the general trend of correlation. Thus, the Gygi data, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Gygi *et al.*

In conclusion, the Examiner has not shown that a lack of correlation between gene amplification and protein over-expression. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. Since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants submit further exemplary articles to show that, contrary to what the Examiner asserts, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (*Mol. and Cell. Proteomics*, 2002, Vol.1, pages 37-45, copy enclosed) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (*Cancer Res.*, 2002, Vol. 62, pages 6240-45, copy enclosed) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (See page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, Vol. 99, pages 12963-12968, copy enclosed) who studied a series of primary human breast tumors and showed that "62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis declaration, overwhelmingly show that gene amplification influences gene

expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO274 proteins and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Assuming *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient

with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO274 polypeptide, for example, in detecting over-expression or absence of expression of PRO274. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

Hence, these data clearly support a role of PRO274 as a lung tumor marker. Accordingly, Applicants request that the present 35 U.S.C. §101 and §112, first paragraph, rejections to the pending claims be withdrawn.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 78-70 are rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ..., one skilled in the art would not know how to use the claimed invention".

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claim 67 renders the rejection of this claim moot.

In response to the rejection under 35 U.S.C. §101, Applicants have shown above that the specification discloses a substantial, specific and credible utility for the PRO274 polypeptide. Further, without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional

applications, Claims 28-32 (and, as a consequence, those claims dependent from the same) have been amended to recite " wherein the nucleic acid encoding the polypeptide is amplified in lung tumors." Since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation based on the general knowledge in the art at the time the invention was made. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. §2164.01.

In view of the discussions above regarding the utility of the polypeptides, Applicants submit that Claims 58-66 and 68-70 satisfy the enablement requirement because one skilled in the art would know how to make and use the claimed polypeptides. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-62, 69 and 70 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of sufficient written description. The Examiner alleges that the claims are directed to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to the polypeptide of SEQ ID NO: 7, but the claims do not require that the polypeptide possess any particular biological activity, conserved structure or other distinguishing feature. Thus, the Examiner notes that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Claims 58-62 (and, as a consequence, those claims dependent from the same) have been amended to recite "wherein the nucleic acid encoding the polypeptide is amplified in lung tumors." This biological activity, coupled with a well defined, and relatively high degree of

sequence identity are believed to sufficiently define the claimed genus, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. §102(b)

The Examiner noted that the priority of the instant application is set at October 15, 2001. As discussed above, Applicants respectfully submit that the effective filing date of the present application is February 11, 2000.

Claims 58-68 are rejected under 35 U.S.C. §102(b) as being anticipated by Ho *et al.*, Science, Vol. 289, pp 265-270 (publication date July 14, 2000). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the cancellation of Claim 67 renders the rejection of this claim moot.

As discussed above, the pending claims of the instant application are entitled to the effective filing date of February 11, 2000, and hence, Ho *et al.* is not prior art under 102(b) since its publication date is after the effective priority date of this application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. §103(a)

Claims 69-70 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ho *et al.* in view of Hopp *et al.*, U.S. Patent No. 5,011,912. Applicants respectfully traverse this rejection.

As discussed above, Applicants are entitled to the effective filing date of February 11, 2000. Therefore, the primary reference, Ho *et al.* is not prior art. Thus, Applicants respectfully submit that the instant claims are not obvious over Ho *et al.* in view of Hopp *et al.* Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C8**).

Respectfully submitted,

Date: November 18, 2004

By: _____
Anna L. Barry (Reg. No. 51,436)

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